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Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Attention: Charles Ganley, MD, Director
Division of OTC Drug Products (HFD-560)
Food and Drug Administration

RE: Docket No. 77N-0094, CP 15
Internal Analgesic, Antipyretic and Antirheumatic
Drug Products for Over-the-Counter Use

FDA February 5, 2002 Letter - Points of Clarification

Dear Dr. Ganley:

Reference is made to the Agency's February 5, 2002, letter to Bristol-Myers Squibb (BMS) in reply to our August 1, 2001, meeting request and draft clinical study proposal.

BMS would appreciate clarification of several key clinical study design issues identified in the Agency's letter. Specifically, we would like additional feedback on FDA Comments 3 and 7. We have outlined our questions in the attached document, which also serves as a partial response to the Agency's letter.

Following resolution of the key design issues, we intend to submit a full protocol for review, prior to initiation of the clinical trial.

For ease of reference, we have included copies of the Agency's February letter and our original protocol outline, which was submitted to the docket on August 1, 2001 (CP 15).

If you have any questions or comments regarding this submission, please contact me at (908) 851-6126.

77N-0094 LET 143

Sincerely,

Donna Coughlin for

Rich Cuprys
Senior Director, Regulatory Affairs
Bristol-Myers Squibb Company
Worldwide Consumer Medicines
1350 Liberty Avenue
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Enclosure
cc: Walt Ellenberg, Ph.D. (HFD-560)

BMS PRELIMINARY RESPONSE TO FDA's FEBRUARY 5, 2002 LETTER

This document represents a partial Bristol-Myers Squibb (BMS) response to the Agency's letter dated February 5, 2002. It outlines the key clinical study design issues that BMS would like clarified.

Bristol-Myers Squibb has carefully considered each of the Agency's comments and agrees with FDA Comments 1 and 2. We would appreciate additional feedback on FDA Comments 3 and 7, as noted below. Following resolution of the key design issues, we intend to submit a full protocol for review, prior to initiation of the clinical trial.

FDA Comment No. 1

"For the purpose of establishing the caffeine dose response, the comparison of efficacy between the aspirin/acetaminophen/caffeine (AAC) combinations and acetaminophen 1000mg is not very informative. The primary objective of the study should be the evaluation of the relative efficacy of the AAC combinations to placebo and with each other."

BMS Response

BMS agrees with the Agency that the primary objective of the study should be the evaluation of the relative efficacy of the AAC combinations to placebo and with each other. Therefore, we have eliminated the active comparator, acetaminophen 1000mg, from the study design (please refer to Table 1, Comparison of Original and Revised Clinical Designs).

FDA Comment No. 2

"To fully assess the adjuvancy of caffeine, the study should include an aspirin 500mg/acetaminophen 500mg arm to assist in the assessment of the dose response relationship between aspirin 500mg/acetaminophen 500mg/caffeine 65mg and aspirin 500mg/acetaminophen 500mg/caffeine 130mg."

BMS Response

BMS agrees with the Agency and we have added an AAC 0 (aspirin 500/acetaminophen 500) arm to the study design (please refer to Table 1, Comparison of Original and Revised Clinical Designs).

Table 1

Comparison of Original and Revised Clinical Designs

	ORIGINAL (August 2001)	REVISED (July 2002)
OBJECTIVE	Demonstrate a statistically significant difference between AAC 65[a] and APAP 1000[b] Compare AAC 130[c] to AAC 65	Demonstrate a positive dose-response relationship (slope >0) between AAC 0[d], AAC 65, and AAC 130.
DESIGN	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, single-dose	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, single-dose
PAIN MODEL	Tension Headache	Tension Headache
TREATMENT ARMS	AAC 130, AAC 65, APAP 1000, Placebo	AAC 130, AAC 65, AAC 0, Placebo
SAMPLE SIZE	1600	1000

[a] AAC 65 = Aspirin 500mg/Acetaminophen 500mg/Caffeine 65mg
[b] APAP 1000 = Acetaminophen 1000mg
[c] AAC130 = Aspirin 500mg/Acetaminophen 500mg/Caffeine 130mg
[d] AAC 0 = Aspirin 500mg/Acetaminophen 500mg

FDA Comment No. 3

"It is not clear that the results from a headache study can be used to support the other general claims available for internal analgesics. Caffeine may have unique benefits in a headache model that may not be apparent in other pain models (e.g. dental pain models). For this reason, the agency recommends that another model be used to assess the dose response for caffeine as an adjuvant."

BMS Response

BMS has previously demonstrated the efficacy of AAC in multiple pain models, including dental, postpartum and tension headache pain. These data have been accepted by the Agency as having established general claims available for internal analgesics.[1] As efficacy has already been established, the objective of the proposed trial is to demonstrate an incremental benefit of caffeine 130mg relative to caffeine 65mg. We believe that in this setting, one trial, in the most sensitive model (tension headache) is the optimal way to address this issue. Similarly, we believe that it would be reasonable to extrapolate results from the headache model to other OTC pain models, since caffeine has already been shown to be a safe and effective analgesic adjuvant in those models.

BMS agrees that caffeine may have unique effects in the tension headache model. BMS data show that caffeine adjuvancy is demonstrated more consistently in tension headache than dental pain.[1,2] The standardized treatment difference (Δ/σ), for AAC vs. APAP alone, and APAP/CAF vs. APAP alone, was consistent across the 7 tension headache studies, ranging from 0.17 to 0.30. However, the standardized treatment difference observed in 5 dental pain trials was much less consistent, ranging from 0.04 to 0.25.

Since tension headache is a more sensitive model for demonstrating caffeine adjuvancy, it is anticipated that it will also be more sensitive for showing the incremental benefit of caffeine 130mg relative to caffeine 65mg.

It is generally accepted that the most sensitive model available be used to establish efficacy/dose response. These results may often be generalized to patients with similar conditions. For example, congestive heart failure (CHF) studies often enroll patients with severe CHF. These results may then be generally extrapolated to support treatment in patients with moderate and mild CHF. This methodology and extrapolation are also common practice in many other models, *i.e.*, angina, hypertension etc. Similarly, we are proposing to utilize the more sensitive model, tension headache, for our trial and believe that the results in tension headache should be generalizable to other OTC pain states.

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[1] Docket 77N-0094, C133, Vol. #120, December 21, 1988 (4 tension headache, 2 dental trials)
[2] Docket 77N-0094, SUP36, Vol. #159-177, November 16, 1989 (2 tension headache trials, 1 dental trial) and CP 15, Vol. #236, July 30, 2001 (1 tension headache trial, 2 dental trials)

***BMS Question 1*: BMS believes one study in the tension headache model is sufficient to demonstrate the incremental benefit of caffeine 130mg, and the results may be extrapolated to general claims for OTC internal analgesics. Does the Agency concur?**

FDA Comment No. 7

"In order to demonstrate a desired treatment effect in analgesic trials, the sample size of the treatment groups is traditionally 50 subjects per study arm in single ingredient studies. Combination products usually contain 80-90 subjects per study arm. Please explain why 400 subjects per arm are needed."

BMS Response

BMS recognizes that a sample size of 50 is usually sufficient to demonstrate a treatment effect in single ingredient analgesic studies and that combination products usually require 80 - 90 subjects. However, in the proposed study comparing varying doses of an analgesic adjuvant, rather than an analgesic, treatment differences are expected to be smaller than in traditional analgesic studies. Based on our evaluation of available data, larger numbers of subjects are required (250 subjects per treatment arm).

BMS clinical trial data (4 large, well-controlled crossover trials, studying more than 1700 subjects, comparing AAC 130, APAP 1000, and placebo), demonstrated a statistically significant, though modest,[3] therapeutic gain from APAP 1000 to AAC 130, (the standardized treatment means difference $\frac{\Delta}{\sigma} \approx 0.25$). Acetaminophen and aspirin have been deemed equipotent analgesics, and it is expected that the analgesic effect of AAC 65 will fall between that of AAC 130 and AAC 0. Therefore, the estimated sample size[4] (which is a function of the variance, magnitude of difference to be detected, and desired power) needed to detect a positive slope is 250 per treatment group (AAC 130, AAC 65, AAC 0, and placebo), for a total of 1000 subjects.

BMS Question 2: BMS plans to conduct a 1000 subject dose response study in the tension headache model to demonstrate the incremental benefit of caffeine 130mg. Does the Agency agree that the sample size is appropriate for the study objective of demonstrating a statistically significant positive dose response?

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[3] Cohen J, Statistical Power Analysis for the Behavioral Sciences, Revised edition, Academic Press, New York, 1977

[4] Guideline for the Clinical Evaluation of Analgesic Drugs, US Department of Health and Human Services, Public Health Service, Food and Drug Administration, Revised December 1992